REMARKS

Applicant thanks the Examiner for reconsidering the Restriction Requirement and examining all the pending claims together.

Claims 32-72 were examined and rejected under various grounds as discussed below.

Claim 32 is amended to incorporate the limitations of claims 33 and 34 which, accordingly, are being canceled.

Claims 44-48 are amended to overcome an indefiniteness rejection.

Claim 39 is being amended to correct a typographical error ("cytidilic" acid). Claim 49 is being amended voluntarily to introduce "cytidylic acid" and "guanylic acid" for the sake of consistency with claim 39.

Claims 32 and 35-72 are now pending. No new matter is being introduced, and entry of these amendments are respectfully requested.

I. *REJECTIONS* UNDER 35 *USC* § 112, 2nd PARA (Indefiniteness)

Claims 39-48 and 53 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite

First Rejection

Claims 39-43 were alleged to be vague and indefinite because it was unclear whether the GC content is the total GC content from C1 and C2. The Office requested clarification

Applicant's Response

Applicant believes that there should be no concern regarding the clarity of this language because if the GC content of C1 is >50%, then so must be the GC content of C2. Because they are capable of hybridizing, they contain complementary sequences. If the GC content of C1+C2 >50%, then the GC content of C1 as well as the GC content of C2 is > 50%, again due the fact that they are complementary to one other. As an example, the Office's attention is directed to para. [0236] of the present published application, *e.g.*, SEQ ID NO:63 and 64 in the Table (reproduced in part below); the bold, underscored parts of the sequences are the clamp segments that are complementary to each other (when the indicated 'order' of one sequence is reversed, of course).

Therefore, it would be proper to withdraw this ground for rejection.

"[0236] The following probes have been used:

SEQ ID #	Locus	Probe no	Length (bp)	5' HEX
63	34	03F481(1A)	67	GCCGGCGGGCCCGGCCGGCGGATGAGTCCTGAGTAACGCCTTCA TATTGATGGTTTTGTTTTTGTT A
64	34	03F482(1B)	65	GCCGGCGGGCCCGGCCGGCGGATGAGTCCTGAGTAACGTTCATA TTGATGGTTTTGTTTTTGTTG

..."

Second Rejection

Claims 44-48 were considered indefinite because the phrase "comparable length" is allegedly unclear.

Applicant's Response

The claims have been amended to read "the same length," so this rejection may be withdrawn.

Third Rejection

Claim 53 was considered indefinite because the phrase "stuffer sequence" is allegedly unclear.

Applicant's Response

"Stuffer sequence" is defined in the specification. See para [0041] of published application. It is a nucleotide sequence that serves the role of imparting a length or mass difference between the probes (a probe which includes it and a probe which does not). Therefore it would be proper to withdraw this rejection.

II. REJECTION UNDER 35 U.S.C. § 102 (Lack of Novelty)

Claims 32-33, 35-41, 44-52, 54-56 and 58-60 were rejected under 35 U.S.C. 102(b) as anticipated by Hogan *et al.* (U.S. Pat. 5424413, Jun. 13, 1995). (hereinafter, "Hogan"). Applicant notes that claims 34, 42, 43, 53, 57, and 51-72 are free of this rejection.

Hogan was applied for the reasons outlined below (among others set forth in the Action).

- Discloses a nucleic acid hybridization probe and method of its use.
- The probe comprises two separate target-specific regions that hybridize to a target nucleic acid sequence and at least two distinct arm regions that **do not** hybridize with the target but possess complementary regions that make them capable of hybridizing with one another (citing col. 1, lines 51- 58 and Fig. 2A) to form a duplex in the presence of target nucleic acid (citing col. 1, lines 58-66 and col. 2, lines 59-62).

- The GC content of both arms ranges from 50%-100% (Fig. 2A). The GC content of some arms is >60% (citing Fig. 3A, 132 strand) or >70% (citing Fig. 3B, 135 strand).
- Cl or C2 comprises at least one C nucleotide more than the number of C nucleotides in T1 or T2 (citing Fig 2A, strand 2) or at least two, three or four G nucleotides more than the number of G nucleotides in T1l or T2 (citing Fig. 2A, strand 1) or at least five G nucleotides more than the number of G nucleotides in T1 or T2 (see Fig. 18, strand 1).
- The length of the arm is 8 - 20 contiguous complementary bases (citing col. 8, lines 9-11).
- The arm region is designed to have a site for extension by a polymerase (citing col. 21, lines 46-48 and col. 38, lines 40-44 (which the Office relates to Applicant's claim 23).
- The regions complementary to the target include a variety of mismatches, some of which are located at the ends of the strands (citing Fig. 13 and col. 19, lines 47-50).

The Action further states that **Hogan** disclose a set of probes (comprising three probes) in which the 135 strand is interpreted as a third probe having a target hybridization region and an additional mismatch; a third probe is allegedly distinct from another two probes (citing Fig. 7).

- A group of probes (at least two pairs of which are involved; see Fig. 6C, 6D, Fig. 7) has an arm region with a unique sequence, so that they form a "unique combination" (citing Fig. 7).
- A target is a nucleic acid sequence that includes essential sequences in the genome of a pathogenic organism, essential mRNA sequences produced by a pathogenic organism, and essential sequences in cancer cells (see col. 4, lines 60-64).

Based on the above characteristics, the Office concluded that the teachings of **Hogan** anticipate the indicated claims.

Applicant's Response

Applicant has amended claim 32 to incorporate the limitations of claims 33 and 34 (which are being canceled). The rejection was not applied to claim 34, also canceled. Based on these amendments, claim 32 and its dependent claims are now novel over **Hogan,** thereby overcoming this ground for rejection.

III REJECTIONS UNDER 35 U.S.C. § 103 (Obviousness)

Claims 34, 42-43, 57, 61-72 were rejected under 35 U.S.C. 103(a) as being obvious over **Hogan** as applied above, in view of Zhang *et al.* (5,876,924, issued March 2, 1999). (hereinafter, **"Zhang"**)

Admittedly, Hogan did not disclose

- That the T1 and T2 segments of the probe are capable of being ligated to each other when hybridized to S1 and S2 as recited in claim 34,
- a junction site between S1 and S2 as recited in claim 57, and
- the method step (c) and (d) for detection of a target nucleic acid in a sample as recited in claims 61-63, and 67.

Zhang was cited for its alleged disclosure of "an improved method" which enables rapid, sensitive and standardized detection and quantitation of nucleic acids from pathogenic samples from a patient (col. 3, lines 11-15). The method allegedly applies a pair of non-overlapping oligonucleotide amplification probes (col. 3, lines 62-66) which Zhang calls "capture/amplification" probes and an amplification probe (see col. 3, lines 66-67). These are said to be complementary to adjacent regions of a target (col. 4, lines 3-8) and do not overlap (col. 4, lines 8-9). The two probes are joined by a ligating agent (col. 4, lines 9-11). In the method the ligated amplification sequence is directly detected (col. 4, lines 16-19), and the two amplification probes may be ligated to form contiguous sequence that is then amplified (col. 4, lines 24-26).

According to the Office, a skilled artisan would have been *motivated* to construct a probe comprising the terminal segments of the **Zhang** probe which can be ligated after the terminal segments are hybridized to a target nucleic acid at an adjacent position. The motivating factor is allegedly the notion that the assembly of an amplifiable DNA by ligation increases specificity and enables detection of a single mutation in a target (col. 3, lines 33-33). The Office concluded that it would have been *prima facie* obvious to include a terminus on each oligo probe which is ligatable when that terminus is hybridized to the target at an adjacent position.

The Office further alleges that a skilled artisan would have been *motivated* to apply the amplification method taught by **Zhang** because it is "an improved method" (as described earlier) (citing to col. 3, lines 19-27). The Office concluded that it would have been *prima facie* obvious to perform the steps recited in claims 61-69.

The Action does note that **Hogan** does *not* disclose the limitations of claims 42 and 43: GC content (in the arm region) is >80% or between 90% and 100%, respectively. However, attention is focused on the disclosure that the **Zhang** capture/amplification probe has a GC content at least 60%, so that it exhibits minimal secondary structure *e.g.,* hairpin or fold back structure (citing to col. 36, lines 1-3). This leads to the conclusion that a skilled artisan would have been *motivated* to design an oligo probe comprising a GC content >80% or between 90% and 100% as allegedly taught by **Zhang.** The motivating factor is supposedly the notion that the

probes would exhibit minimal secondary structure. So, the Office's conclusion was that it would have been *prima facie* obvious to design an oligo probe with GC content >80% or between 90% and 100% (*i.e.*, as claimed in claims 42 and 43).

The Action further admits that **Hogan** does not disclose a kit comprising probes and reagents for detecting target DNA in a sample (present claims 70-72). However, this is allegedly provided by **Zhang** which discloses a kit comprising probes and reagents for detection of an amplified ligated DNA sequences (col. 25, lines 7-36). The Office alleges that the skilled artisan would have been *motivated* to construct such a kit (as taught by **Zhang)** for convenience sake because this was routine practice in the art. This is the reason that the kit claims (71-72) were considered to be *prima facie* obvious.

Applicant's Response

1. Primary Reference has been removed

In view of the amendments to claim 32, the primary reference (Hogan) is no longer applicable to claims that depend from claim 32. Even if combined with Zhang as a secondary reference, the combination would be legally inadequate to support a *prima facie* obviousness rejection. Therefore, claims 32 and its dependent claims (all the remaining claims except for Claim 70), and independent claim 70 (which was never considered anticipated by Hogan) should be considered free of the § 103 rejection that combines these references.

2. Analysis of Zhang Disclosure

As further support for the patentability of the present claims, a careful consideration of the Zhang disclosure is needed (alone and in conjunction with Hogan). In doing so, one notes the following.

At the top of col. 36 (cited in the Action), Zhang discloses that the **5'** portion of the capture/amplification probes (which is ***not directed to, or specific for, the target***) contains random sequences with GC content of at least 60%. These are there to prevent secondary structure formation, *i.e.*, hairpins or foldback structures. Zhang describes this for two probes that (at their 3'ends) are specific for two different alleles (SEQ ID NO:22 and 23). The AMP probes disclosed at col. 36, lines 57 *et seq.*, which are to be ligated to the capture/amplification probes **do not contain any such a GC-rich region that could serve as a "clamp."**

So Zhang only discloses one end of the probe to be GC-rich which (in theory, and in light of Applicant's disclosure) could be harnessed to serve as a clamp but is never disclosed as such. And although Hogan discloses clamps, they are ones that are "wrongly oriented" and distinct from the clamp of the present probes.

It is important to note that Zhang neither discloses nor remotely suggests that these "one-sided GC-rich" segments could be used to make clamp regions designed to hybridize to the probe at the other end, as is the case with the presently claimed probes (*e.g.*, see those depicted in Applicant's Fig. 1). Interpreted properly, the only thing Zhang can be said to teach is how to make the non-hybridizing parts of the probe, so that:

1. interference with the target nucleic acid is minimized;
2. they provide a different melting/annealing temperature for subsequent amplification; and
3. as already noted, they do not form secondary structures (hairpins, foldbacks, *etc.*).

This is clearly sufficiently distinct from the present invention and insufficient to complement the missing disclosure in Hogan (which reference is no longer applicable to the claims as presently amended). Hence, the present claims cannot be viewed as *prima facie* obvious. Zhang does not compensate for the inadequacies of Hogan in supporting obviousness of the amended claims.

Thus, for the reasons advanced in Sections 1 and 2, above, the Office is urged to withdraw the rejection under § 103(a) of claims 42-43, 57, 61-72 (claim 34 having been canceled).

IV. CONCLUSION

Applicants respectfully request entry of the foregoing claims and Remarks, and reconsideration of the rejections and allowance of the present claims.

Respectfully submitted,

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